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TITLE: Hepatitis C. Virus Infection: Mechanisms of Disease Progression

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**14. ABSTRACT**

An estimated 4.1 million individuals in the USA are chronically infected with the hepatitis C virus. Annually 8,000 to 10,000 of these subjects will die of liver-related complications and approximately 1,000 will require liver transplantation. The United States military have rates of HCV infection similar to the general US population (1.6%). However, it is a younger population and its natural history of HCV infection has not been studied. Therefore, the clinical outcome of HCV-infected military subjects and risk factors contributing to disease progression are largely unknown. Such knowledge is essential for decisions regarding optimal management and prevention of the disease. This study focuses on active duty military subjects infected with HCV, who will be enrolled and observed prospectively over four years (48 months). Liver biopsies are to be performed at initiation if needed and at completion of study to observe for disease progression. Lab evaluation of virologic and biochemical indicators of the disease and detailed information about risk factors, and quality of life are collected by questionnaire every six months. Currently, 95 subjects have been enrolled and 65 subjects are being followed. It is too early to report conclusions on the data in terms of disease progression and potential contributing factors to disease progression specific to this population, as only 19 subjects (15%) have completed the study. However, trends concerning the decision to treat will be discussed. Therefore, the majority of the data presented in this report will be confined to descriptive statistics of the sample to date.

**15. SUBJECT TERMS**
Hepatitis C; virus; liver; cirrhosis HCV RNA; epidemiology; US military

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## INTRODUCTION

An estimated 4.1 million individuals in the USA are chronically infected with the Hepatitis C virus. Annually, 8,000 to 10,000 of these people will die of liver related complications and approximately 20,000 are waitlisted for liver transplantation with 20% actually receiving a new liver. Thus, HCV is a major public health problem. The US military population has rates of HCV infection similar to the general US population with an overall rate of 1.6%. However, it is a younger population and the natural history of HCV infection in the population has not been studied. Therefore, the clinical outcome of HCV infected military subjects is largely unknown. Specific factors in military life have not been studied to observe if they contribute to disease progression. Such knowledge is essential for decisions regarding optimal prevention and management of the disease.

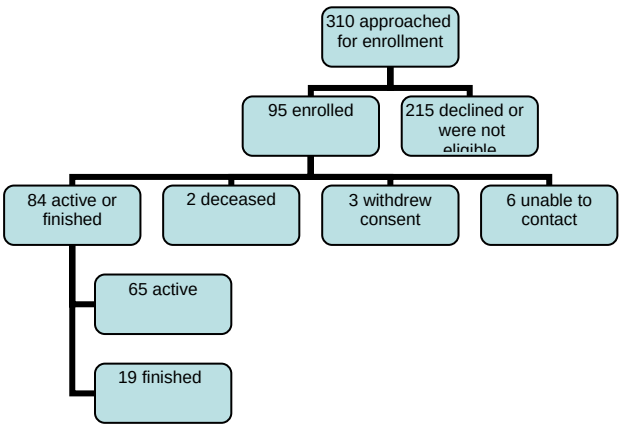
Active duty service members with chronic HCV infection will be enrolled and observed prospectively over four years in this study. Our principal hypothesis is that in active duty members infected with HCV genotype-1, liver disease progresses more rapidly than in subjects infected with HCV non-genotype-1. The effect of other factors that might influence histologic progression of liver disease including age, race, rank, deployment, alcohol consumption, and HCV RNA level will be assessed. To test this hypothesis we have the following specific aims:

- To compare the rate of progression of liver disease based on a histologic severity scale in military subjects infected with genotype-1 to the rate of progression in those infected with non-genotype-1.
- To identify other predictors of progression of histologic liver disease in a military population.
- To determine risk factors for acquisition of genotype-1 compared to non-genotype-1 HCV.
- To describe the natural history of HCV infection in a group of a military population.

## BODY

To date approximately 310 patients have been approached about participation in the study, with approximately 25 patients having been contacted in the last year. Of those contacted, 95 subjects have been successfully enrolled. There are 65 active participants (participants currently being followed) ranging in status from baseline to month 42. Additionally, 19 subjects have completed the study with all but 3 subjects completing at least two-thirds of the visits. In addition, to the 84 active or finished participants, 2 are deceased, 3 withdrew consent and 6 have been unable to be contacted for over 1 year and have subsequently been dropped from the study. (see figure 1) Of those who terminated early, reasons cited included too far to travel and one felt the questions were not relevant, the others were lost to follow up. Enrollment is open and ongoing. We hope to accrue between 86-120 patients total. This goal required downward adjusting in part due to the loss of Balboa Medical Center as an expected participating site. Deployment of active duty to Iraq, Afghanistan, etc. since 2002, as well as staff turnover due to deployment to Iraq in the WRAMC Center for Liver Disease within the past few years has unfortunately created eligible potential subjects being overlooked.

*Figure 1.*



Because of enrollment below our expected subject participation, a previous review had requested that we conduct a sample size analysis to determine the minimum number of subjects in the study to be able to conduct valid statistical analysis. The number of subjects varies between 120 and 160 depending on the difference of study characteristics in the studied groups (genotype 1 vs.. non-1, officer vs.. enlisted, cirrhosis vs.. non-cirrhosis, etc). If the difference is striking (in the order of 25% to 30%) a sample size of 43 subjects per group will be enough. We planned to finish enrollment in October 2006, however, continued staff turnover, deployment, and soldier relocation have delayed this. We continue to ask our NNMC colleagues to send eligible subjects to our Liver Clinic to increase our 'n' to our goal of 120 subjects. A no cost extension will be requested to improve our enrollment figures.

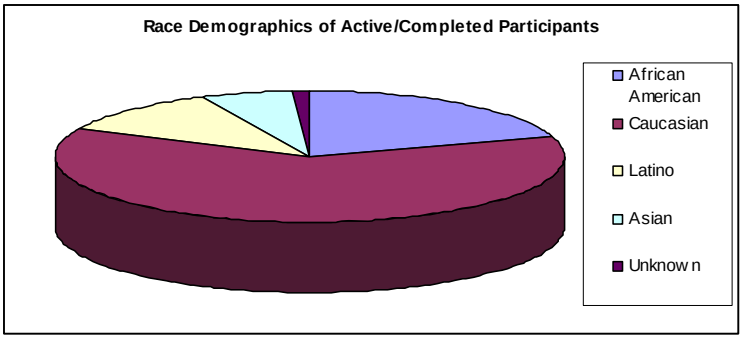
This is not an interventional study, no adverse events have been reported since the last APR.

At this point, 19 subjects (15%) have completed the study. Due to this number being so small, conclusions cannot be made about histological progression until there is complete study data including the second liver biopsy for a greater number of subjects. However, the existing active sample including the 19 completed patients can be described as follows:

**Sample Demographics:**

- 84% of the sample is male.
- The current ages of the subjects range from 20 to 60. The mean age is 44.
- 20% of the sample is African American. 62% are Caucasian, 11% are Latino, 6% are Asian, and 1% are of unknown ethnicity (see figure 2).

*Figure 2.*




- 27% of our sample completed high school, 56% had at least some college, and 16% of the sample had post-graduate education.
- 51% of the sample had a household income of >$50,000, 30% had a household income of $25,000-$50,000, 15% had a household income between $10,000 and $25,000, 1% had a household income of <$10,000, and 3% declined to answer.
- 80% of the sample is enlisted.
- 26% of the sample think they have had HCV for at least 10 years, 66% think they have had it less than 10 years, and 8% of the sample declined to answer or didn't know.

**Baseline Lab/Histology Data:**

By and large the sample does not have indicators of advanced (decompensated) liver disease as evidenced by biochemical indicators. At baseline, the mean PT is 13.47, mean albumin is 4.23, and mean ALT is 102.54.

- 40.3% of the sample had ALT less than 72, which is the high limit for males at WRAMC laboratories.
- 73% of the sample is genotype-1, 21.4% is genotype-non-1, and 1.2% of the sample is unknown.
- 62% of the sample had viral loads >500,000 IU/mL. Of the total sample, 11.3% had viral loads >850,000 IU/mL.

- 21.6% of the sample had no or minimal fibrosis. 28.4% of the sample showed signs of perioportal fibrosis and 28.4% of the sample had bridging fibrosis. 4.1% of the sample had cirrhosis.

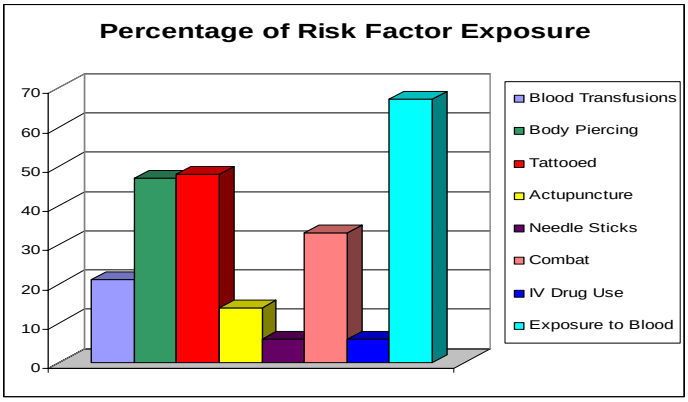
**Lifestyle Factors potentially contributing to disease acquisition or progression:**

- 11% of the sample self reports having a drinking problem now or in the past.
- 11% has had a DUI.
- 26% of the sample have answered one of the CAGE questions affirmatively.
- 66% of the sample has a tobacco use history, but only 27% are current smokers.
- 19% had been incarcerated.
- 38% of the sample has had more than 10 sexual partners.
- 16% has had sexual intercourse with a prostitute.

**Risk Factor Analysis (see figure 3):**

- 21% of the sample has a prior history of blood transfusion.
- 47% has at least one body piercing.
- 48% of the sample is tattooed.
- 14% has had acupuncture.
- 6% has had needle sticks.
- 33% has been in combat.
- 6% of the sample has a past history of IV Drug Use.
- 67% report having had cutaneous exposure to somebody else's blood.
- 64% shared nail trimming instruments.

*Figure 3.*




We were able to examine this preliminary data to see if any trends or patterns emerged, specifically with respect to our aim of determining if there were any specific risk factors for acquisition of genotype-1 compared to non-genotype-1 HCV (see tables 1 and 2). Although not significant, trends emerged suggesting, in general, genotype-1 infected individuals may be more likely to have lifestyle risk factors whereas, genotype non-1 may be more likely to have other risk factors.

*Table 1.*

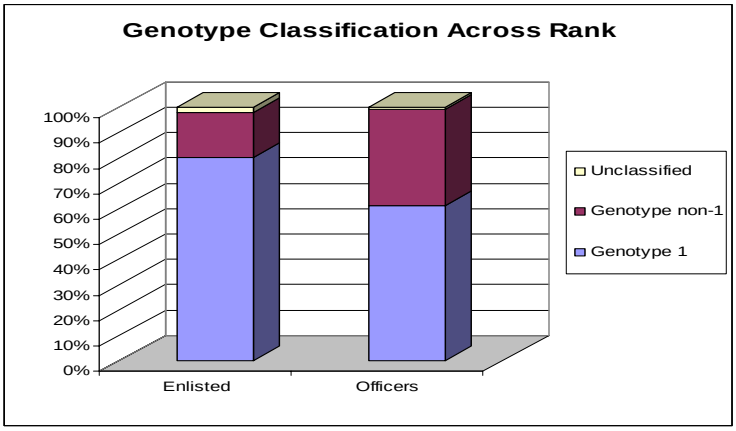
| **Lifestyle Risk Factors** | | | | | | |
|---|---|---|---|---|---|---|
| | **Incarceration** | **IV Drug Use** | **Drinking Problem** | **DUI** | **Sex with >10 Partners** | **Sex w/a Prostitute** |
| ***Genotype-1*** | 14.8% | 5.6% | 9.3% | 13.0% | 37.0% | 18.5% |
| **Genotype Non-1** | 27.8% | 5.6% | 16.7% | 5.6% | 38.8% | 5.6% |

*Table 2.*

| **Other Risk Factors** | | | | | |
|---|---|---|---|---|---|
| | **Transfusion** | **Acupuncture** | **Tattoo** | **Piercing** | **Exposure to Blood** |
| ***Genotype-1*** | 20.4% | 13.0% | 48.1% | 46.3% | 66.7% |
| **Genotype Non-1** | 22.2% | 16.7% | 50.0% | 50.0% | 66.7% |

Looking at the relationship between genotype and demographics revealed that 61.0% of officers were genotype-1 while 80.1% of the enlisted subjects were genotype-1 (see figure 4). This difference was not significant.

*Figure 4.*




**Quality of Life:**

- 19.4% of the sample feels that they have been limited by their HCV in the past two weeks in performing their daily work at least some of the time during the past two weeks.
- 18.1% of the sample feels that their HCV has limited their activities (walking, climbing, stairs, carrying groceries, playing sports) at least some of the time in the past two weeks.
- 43.1% of the sample has had difficulty sleeping at night at least some of the time during the last two weeks.
- 48.6% of the sample worried at least some of the time during the past two weeks that their symptoms will develop into major problems.
- 44.4% of the sample worried at least some of the time during the past two weeks that they might die earlier than expected because of their Hepatitis C.

- 30.6% of the sample experienced emotional stress or strain in their relationships at least some of the time during the past two weeks as a result of their hepatitis C.

These data are generated from the chronic liver disease questionnaire-HCV (CLDQ-HCV), which is asked at baseline and each patient visit. The above results express how subjects (n=95) felt at their most recent visit-regardless of treatment status. An additional Quality of Life questionnaire, the SF-36 of Hepatitis Quality of Life Questionnaire (HQLQ), is also administered at each visit. Upon completion of the study, HQLQ data will be scored by a professional scoring service, therefore, no analysis is available at the time of this report.

**Therapy Outcomes**

Although the subjects enrolled in this study do not receive any anti viral therapy as a part of the study, a number of subjects are/have been enrolled in other studies involving treatment and/or have received such treatment at the WRAMC Liver Clinic. The below statistics were calculated for the 95 patients that were enrolled for the study.

- 62% of the sample has been exposed to an Interferon treatment while participating in this study.
- Of those exposed to Interferon treatment, currently,
    - 66% are currently showing a viral response or have a sustained viral response to the treatment and currently have undetectable HCV viral loads.
    - 32.1% did not respond or relapsed after showing initial response to the treatment.
    - 1.9% has an unknown current status.

## KEY RESEARCH ACCOMPLISHMENTS

Enrolled 95 subjects.

## REPORTABLE OUTCOMES

Incomplete data does not allow for conclusions to be made in this report. However, with the majority of our subject population completing at least one year, this period of time can be examined. Fifty-one (54%) of our subjects received treatment during the first year of the study. We were able to explore this data to see if any differences emerged between those subjects receiving treatment and those not receiving treatment. Trends can be described as follows:

**Average % Changes in Labs After One Year:**

- Subjects Receiving Treatment in First Year
    - ALT decreased 58%
    - Albumin decreased 2.52%
    - Platelets decreased 7.14%
    - Prothrombin Time increased 0.90%

- Subjects Receiving NO Treatment in First Year
    - ALT decreased 1.33%
    - Albumin decreased 0.53%
    - Platelets decreased 5.66%
    - Prothrombin Time decreased 4.66%

**Change in Quality of Life During the First Year:**

- Subjects Receiving Treatment in First Year
    - Depression increased 18%
    - Mood Swings decreased 13.7%
    - Irritability decreased 23.7%
    - Fatigue increased 2.5%
    - Limitations in Daily Work increased 33.5%

- Subjects Receiving No Treatment in First Year
    - Depression increased 100%
    - Mood Swings increased 9%
    - Irritability increased 22.5%
    - Fatigue increased 13.5%
    - Limitations in Daily Work increased 55.6%

Data suggests that laboratory values improve with treatment. In addition, untreated subjects are significantly more likely to report feeling depressed, having increased irritability, and having greater mood swings than those that are treated.

## CONCLUSIONS

Inferences cannot be made about histological progression of hepatitis C in this population as there have only been nineteen (15%) subjects that have completed the study. Until there are more patients with complete study data including the second liver biopsy conclusions are unavailable. However, interesting trends are beginning to emerge with respect to genotype, military rank, risk factors, and the impact of treatment. As more data is obtained, analysis that looks at the other indicators of disease progression such as biochemical markers will also be able to be performed. Additionally, it is hoped that the morbidity and quality of life data will lend insight into an under-researched area of study in this disease process in the active duty military population.

## REFERENCES

None at this time.

## APPENDICES

Not applicable.